CLINICAL PROCEEDINGS OF THE CHILDREN'S HOSPITAL

Washington, D. C.

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Occasionally, the remarks and observations of guest speakers are included in this bulletin when thought to have particular interest. The proximity of the Children's Hospital to the Medical Centers of the Army, Navy and United States Public Health Service affords us the opportunity to invite many distinguished physicians to our conferences.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

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BACKGROUND

THE use of cow's milk, water and carbohydrate mixtures represents one system of infant feeding that consistently, for over three deca has received universal pediatric recognition. No carbohydrate emplo in this system of infant feeding enjoys so rich and enduring a backgro of authoritative clinical experience as Mead's Dextri-Maltose.

Clinical Proceedings

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

VOL. I JULY, 1945 No. 8

SHOULD VITAMIN D BE GIVEN ONLY TO INFANTS?

VITAMIN D has been so successful in preventing rickets during fancy that there has been little emphasis on continuing its use af the second year.

But now a careful histologic study has been made which reve a startlingly high incidence of rickets in children 2 to 14 years o Follis, Jackson, Eliot, and Park* report that postmortem exami tion of 230 children of this age group showed the total prevale of rickets to be 46.5%.

Rachitic changes were present as late as the fourteenth year, a the incidence was higher among children dying from acute dise than in those dying of chronic disease.

The authors conclude, "We doubt if slight degrees of rick such as we found in many of our children, interfere with hea and development, but our studies as a whole afford reason to p long administration of vitamin D to the age limit of our study, fourteenth year, and especially indicate the necessity to suspect a to take the necessary measures to guard against rickets in s children."

*R. H. Follis, D. Jackson, M. M. Eliot, and E. A. Park: Prevalence of rickets in child between two and fourteen years of age, Am. J. Dis. Child. 66:1-11, July 19

SPECIAL REPORT[1]

ERYTHROBLASTOSIS

John E. Cassidy, M.D.[2]

History

Isoimmunization, first noted by Ehrlich and Morgenroth (1) in 1900, means the immunization of a member of a species by another member of the same species. They produced isohemolysins in the goat by injecting erythrocytes of other goats, and their observations showed the possibility that a considerable number of different antigens might exist in similar cells of different individuals in a single species.

The blood of some animals contains antigens related to agglutinogens present in individual human bloods. Pursuing this idea, by immunizing rabbits with Rhesus blood, an immune serum was obtained with which an agglutinable factor different from A, B, M, N or P, was detected by Landsteiner and Wiener (2). This new factor was designated Rh to indicate that Rhesus blood had been used to produce the serum. Further studies showed this property to be present in 85% of white individuals, 98% of colored individuals and in 99+% of the yellow race.

The clinical importance of these observations was noted by Wiener and Peters (3) who studied blood samples from three patients who had shown hemolytic reactions after receiving repeated transfusions of blood of the proper group. They found that the sera of these patients contained anti-Rh agglutinins, while in the blood cells the factor was lacking. This showed that the agglutinogen in question is endowed with the capacity to induce the formation of immune isoantibodies in certain human beings.

Levine and Stetson (4) had reported, shortly before the afore mentioned work, a severe accident following a transfusion of apparently compatible blood in a woman after a stillbirth and offered the explanation that the patient had been immunized by an antigen in the dead fetus, inherited from the father. This hypothesis then assumed that isoimmunization can result from pregnancy. Wiener and Peters (3) pointed out that every reported hemolytic reaction to a first transfusion had ocurred in a woman pregnant at the time or who had recently had a child. Other cases of transfusion reactions attributable to isoimmunization of pregnancy were reported by Levine and Katzin (5).

In 1941 the pathogenesis of hemolytic anemia of the newborn was

[1] Presented at the Clinical Conference, Children's Hospital, Washington, D. C., on July 1, 1945.

[2] From the laboratory service of Drs. Lindsay, Rice and Selinger.

clearly defined by Levine (6) and his co-workers, when they demonstrated the role of the Rh factor of Landsteiner and Wiener. In the usual case the mother is Rh negative, that is there is an absence of the Rh factor, the infant and father are Rh positive. This holds true in about 90% of the cases. Due to some defect in the placenta some of the fetal blood escapes into the maternal circulation and in sensitive mothers this stimulates the production of anti-Rh isoantibodies which filter back through the placenta into the fetal circulation. It may be that they are then picked up by the fetal cells and stored and only when the tissues are saturated do the antibodies combine with and destroy the fetal red blood cells. Depending on the amount of destruction this may result in intrauterine death. When the amount of antibodies is not excessive the baby is born alive and may have a normal blood picture. Then for some unknown reason the antibodies are set free to hemolyze the red blood cells.

In the 10% of mothers of erythroblastotic babies who are Rh positive, the process may be explained by the fact that the mother is a different subtype Rh than the fetus, that is Rh^1, Rh_1, or Rh^2. In some of these cases the Hr factor may provide the explanation. This was first described by Levine, Javert and Matzen (6, 7) who found that the serum of an Rh positive mother of an erythroblastotic infant agglutinated all Rh negative bloods and those Rh positive bloods which did not react with anti-Rh^1 serum. Hr was selected as the symbol to indicate that it was opposite to Rh because it is present in all Rh negative bloods. Isoimmunization in other cases in this group may be due to other factors such as A, B, M, or P. Polages (8) recently reported two cases of erythroblastosis in which the Rh factor and its variants were excluded as possible immunizing antigens and in both of which very high anti-A agglutinin titers were obtained in the mother's serum.

In 1932 Diamond, Blackfan, and Baty showed very definitely that hydrops fetalis, icterus gravis, and anemia of the newborn are related and that a variation in the severity of the underlying pathological process produces a different symptom complex. This process as we now know is hemolysis of fetal red blood cells with compensatory extra-medullary red cell formation.

Cases

In the past eleven years there have been 29 cases of erythroblastosis fetalis admitted to the hospital, 26 of these in the past six years, 13 of them in the past year. Twenty-seven of these were white, two were colored, which is what one would expect when the low incidence of Rh negative individuals in the colored race is recalled. The distribution of types is seen in the chart. Most of our cases have been either the simple anemia or

icterus gravis, only one instance of hydrops fetalis being seen. In the first group, simple anemia, there were seven cases with three deaths. Two of these three received no treatment—one having been seen by a physician for the first time since birth at the age of two weeks. She was rushed to the hospital but died within thirty minutes, before blood could be obtained and autopsy revealed findings indicative of a severe anemia and marked extra-medullary erythropoiesis. Another case was one transferred to this hospital at the age of seven days because of increasing pallor and a red blood cell count below one million. This infant died without receiving any blood even though he was in the hospital for thirty hours. This case brings home the close cooperation needed between the clinicians and the

Distribution of Types

TYPES	SIMPLE ANEMIA	ICTERUS GRAVIS	HYDROPS FETALIS	TOTAL
Number of cases	7	21	1	29
Lived	4	17	0	21
Died	3	4	1	8

CHART 1

Rh Factor Studies

	Rh+	Rh−	ANTI Rh	
			Yes	No
Patient	24	1		
Mother	0	25	8	9
Father	22	0		

CHART 2

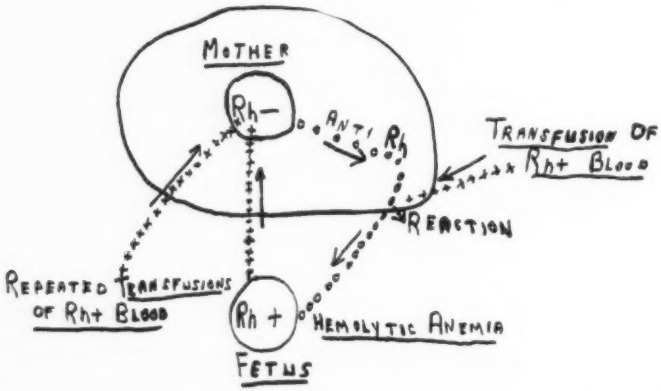
laboratory. The third of these was an infant treated in another hospital and then transferred here. A diarrhea developed and in a short time caused the infant's death.

In the second group, icterus gravis, there were 21 cases, 4 of which died. Once of these was complicated by a severe congenital heart disease. There was one case of hydrops fetalis which lived for only thirty-six hours.

Rh factor studies were done in 25 of the 29 cases. In all of them the mother was Rh negative, which is not in agreement with the observations of others. In all but one the infant was Rh positive. It is possible that the testing sera used when this latter determination was made was not capable of picking it up as a positive. We have been unable to check this with our more potent and accurate sera.

Attempts were made to demonstrate anti-Rh in the mother's blood in 17 cases and we were successful in 8, the titer being low in all but one in which it was 1:160.

In the usual case there is nearly always a history of preceding pregnancies, with at least one normal infant before an affected one appears. In other words a certain amount of sensitization and building up of isoantibodies must occur. This sensitization may be carried out by the presence of an Rh positive fetus or by transfusions of Rh positive blood. Sensitization and production of antibodies may occur with the first Rh positive fetus but this is not the more common occurrence.



ISOIMMUNIZATION BY Rh FACTOR

CHART 3

In our group we have two instances where we believe sensitization may have been brought about by transfusions of Rh positive blood. One mother miscarried at three months during an attack of pneumonia. At this time she received two blood transfusions, without any reaction. We were able to test the donors for Rh at a later date and one was found to be Rh positive, the other, the patient's brother, was Rh negative. She became pregnant one year later and gave birth to an eight months premature infant with hydrops fetalis. This mother is Rh negative and her husband Rh positive. About a year and a half ago she again became pregnant and it was at this time that she first came under our care. We began to test her blood for anti-Rh during the fifth month of this pregnancy and did so at regular intervals thereafter. At first antibodies could be demonstrated only in undiluted serum but towards the end of the seventh

month the titer began to rise and in the first week of the eigth month she went into labor and was delivered of a dead fetus.

The other case had a similar history, miscarriage at three months associated with uterine bleeding which necessitated two blood transfusions. Six months later she again became pregnant and went to full term, but the infant had hemolytic anemia icterus gravis type. We were unable to trace the blood donors and check them for the Rh factor. The mother is Rh negative and the baby and father Rh positive.

In all the other cases, except two, the affected baby had been preceded by at least one pregnancy with a normal fetus. In these two cases there was no history of blood transfusions at any time and it was the first pregnancy.

These facts stress the importance of the necessity of paying attention to the Rh factor when transfusing a patient, especially a female. In the first case mentioned above it is probable that if the mother had not been transfused with Rh positive blood, thereby sensitizing her to the Rh factor, she would have had a better chance of having a normal baby or at least one with a less severe form of the disease.

Diagnosis

The presence of any of the symptoms of the three complexes leads one to suspect the condition. Hydrops fetalis is evident. In icterus gravis the jaundice is present at birth or develops within the first forty-eight hours and is accompanied by an anemia, which is progressive in character. In the simple anemia of the newborn, the infant may be apparently well for the first few days and then the anemia manifests itself and can be a very rapid affair once it begins. The blood picture usually shows a hyperchromic macrocytic type of anemia with a decrease in the platelets and the presence of varying numbers of erythroblasts. But the presence of erythroblasts in the peripheral blood is not essential for the diagnosis. A more important point is the Rh negativity of the mother, and even then it should be kept in mind that not all Rh positive infants born of Rh negative mothers will have hemolytic anemia of the newborn. Also it should be remembered that in a small per cent of these cases the mother will be Rh positive. The absence of demonstrable anti-Rh in the mother's serum does not rule out the condition, but its presence is a very strong point in favor of it.

Syphilis, sepsis, and congenital anomalies of the biliary tree are the most common diseases apt to be confused with hemolytic anemia of the newborn.

These infants may go on to develop an obstructive type of jaundice due to inspissation of the breakdown products of the red cells in the smaller biliary radicals. This is really an intra-hepatic biliary obstruction. There were two such instances in our group, both of which recovered. One of

these deserves more detailed mention. The infant was brought here from another hospital because of its hemolytic anemia. The mother was Rh negative and her blood contained Rh isoantibodies, the baby was Rh positive. She was treated by transfusions of Rh negative blood to which she responded fairly well. But her jaundice persisted and she developed acholic stools. Her general condition failed to improve and surgery was performed, a cholecystjejunostomy being the procedure of choice. It was not possible to explore the bile ducts because of the patient's poor condition. Two weeks following the operation she began to gain weight, the jaundice cleared and traces of bile were found in the stool. It is probable that surgery did not relieve an obstruction in this case because of the length of time it took for the bile to appear in the feces.

Treatment

It is advisable that infants with hemolytic anemia of the newborn be kept from receiving breast milk from their mothers. Davidsohn (9) demonstrated sizable titers of anti-Rh in a number of specimens of breast milk from mothers of erythroblastotic infants as did Witebsky (10, 11).

Whether these antibodies can be absorbed from the gastro-intestinal tract has not been absolutely proven but clinical evidence seems to substantiate this. One of the cases in our group will illustrate this point. The baby was Rh positive, the mother Rh negative. Jaundice appeared twenty-four hours after birth. Frequent checks were done on the blood and the hemoglobin and red blood cells maintained a satisfactory level. Examination of the blood of the mother revealed anti-Rh agglutinins present in a low titer but none were demonstrable in the breast milk (Dr. Diamond, Blood Grouping Laboratory, Boston). In view of this the mother was allowed to nurse the baby but on discharge from the hospital was instructed to return in one week for a check-up. She failed to do this and was next seen five weeks after discharge at which time the hemoglobin and red blood cells of the baby had dropped to 7 gms. and 2,6000,000 respectively. Breast feedings were immediately stopped and three transfusions of type O Rh negative blood were given, with a good response. Off hand one cannot absolutely say that the anemia was due to absorption through the intestines of Rh antibodies from the breast milk, but it certainly is suggestive.

The treatment of acute hemolytic anemia of the newborn by repeated transfusions of suitable Rh negative blood has brought about a definite decrease in the mortality. The theory of Levine et al. makes possible a more rational transfusion therapy for the disease. The most suitable blood is that from a normal Rh negative donor the same type as the infant. His cells will contain no Rh factor and will not be sensitive to the action

of antibodies and his serum contains no anti-Rh isoantibodies. If an Rh positive donor is used the cells are susceptible to the antibodies producing the disease in the infant and will be destroyed by it. Mollison (12) traced the fate of donor's blood in infant's circulation by the method of differential agglutination and demonstrated that while Rh negative blood survived for periods up to three months, Rh positive blood was often eliminated within 4 or 5 days.

Similar studies were done on one of the patients in our group. She was a type B and was transfused with type O Rh negative blood. Beginning

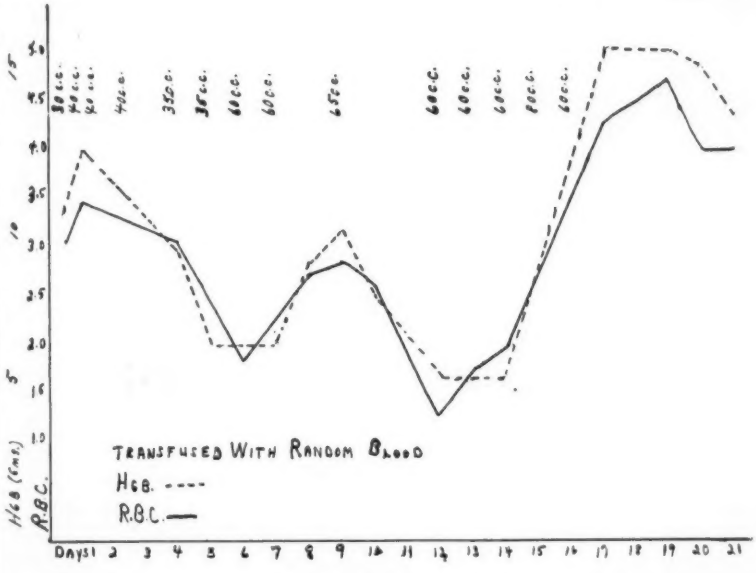


CHART 4

at the end of the fourth week red blood cell counts by the differential agglutination method were done. At this time the infant's own cells type B, were less than one million per cubic millimeter and the transfused type O Rh negative cells were almost two million per cubic millimeter. Seventy-five cubic centimeters of type O Rh negative cells were then given and three weeks later the type O cells numbered two and one half million per cubic millimeter. From then on the infant's own cells increased in number more rapidly. At the end of eighty days there were still over one million per cubic millimeter of the transfused cells in the circulation.

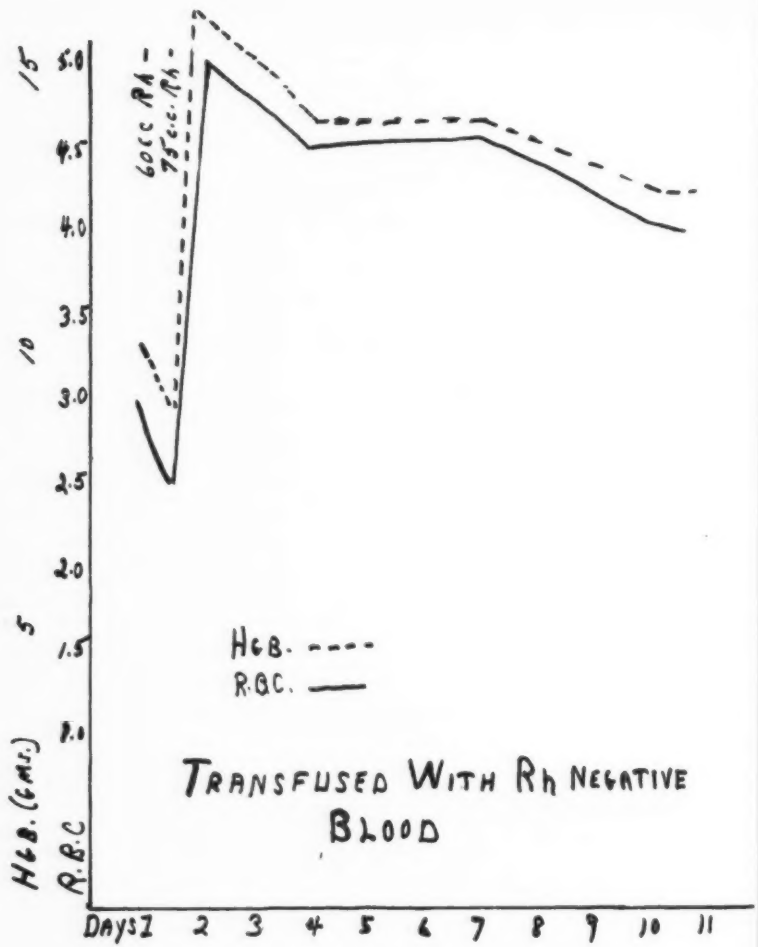


CHART 5

In those cases where the mother is Rh positive the safest thing to do would be to transfuse the infant with her washed red blood cells, because they would be insensitive to the action of the antibodies.

Blood transfusion in these cases is an emergency measure. It stands to reason that if an Rh negative donor is not immediately available, rather

than give no blood at all an Rh positive donor should be used to tide the patient over until one can be obtained.

In our group of cases there were eighteen treated with Rh negative blood and six with random blood. In the former group the average number of transfusions was three and the average amount transfused one hundred and ninety-five cubic centimeters as compared to an average number of eleven transfusions and an average amount of seven hundred and sixty cubic centimeters in the latter group.

Two specific cases will illustrate still further this contrast in therapy. The first was admitted to the hospital within twenty-four hours after birth because of jaundice and anemia. The initial blood count revealed ten grams of hemoglobin and three million one hundred thousand red cells with ten thousand erythroblasts. Transfusion therapy was begun immediately. In the first five days the patient received six transfusions of blood from her father, who we now know is Rh positive. We have been unable to trace down and test the other donors for the Rh factor but it is reasonable to assume that most of them are positive. In all, fifteen transfusions were given in a space of seventeen days before the red cells and hemoglobin reached a normal level and remained there.

The second case was admitted to the hospital twenty-four hours after birth because of jaundice and anemia. The initial red blood cell count was three million, the hemoglobin ten grams with twenty thousand erythroblasts. This infant resembled the previous one clinically. Two blood transfusions of normal Rh negative blood were given. Twelve hours after the first the red cell count had dropped four hundred thousand but rose promptly after the second one and remained within normal range.

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ROCKY MOUNTAIN SPOTTED FEVER

Case Report No. 26

Dr. Mary Warner J. T.—45-4322

J. T., a five year old white male, was admitted to the hospital on May 27, 1945 with the chief complaint of sustained high fever for ten days. The onset of the fever was accompanied by vomiting which persisted for two days. A rash appeared on the arms and legs on the fifth day of illness. The patient complained of aches and pains in his back and legs for three days prior to admission. Anorexia and drowsiness were present from the onset. Three ticks firmly attached to the skin were found on the back of the patient's neck five days before the appearance of the fever. The boy lives in a tick infested area in Upper Marlboro, Maryland. The past medical and family histories were non-contributory.

On admission the physical examination revealed a well developed but undernourished white male of five years who appeared toxic and very drowsy. He could however, be aroused readily and answered questions intelligently. The temperature was 104°. The skin was hot and flushed and over the extremities, including the palms of the hands and the soles of the feet, was a discrete papular rash. A few papules were found on the trunk. There was marked enlargement of the posterior cervical and inguinal lymph nodes. Nuchal rigidity, Brudzinski's and Koenig's reflexes were present. The throat was negative. The lungs were clear to percussion and auscultation. The heart action was rapid and regular. Liver or spleen were not palpable. The impression on admission was Rocky Mountain Spotted Fever with meningeal irritation.

Laboratory examination showed a red blood count of 3,600,000 with 10 gms. Hgb. The white-cell count was 6,150 with 42% neutrophils and 58% lymphocytes. Urinalysis was negative. The spinal fluid contained 75 leukocytes with 70% lymphocytes and 30% mature white-cells; protein and sugar content were normal. Blood culture was negative.

Fifteen days after the onset of illness, the blood serum agglutination reaction with Proteins OX19 was negative, but five days later, it was found to be positive in dilutions of 1:20 through 1:320. The complement fixation test for Rocky Mountain Spotted Fever was also positive.

The treatment was entirely supportive. Three hundred c.cms. of 5% dextrose in saline was given intravenously on the second day to combat mild dehydration. Fluids were urged. The temperature remained at 104° for two days and returned to normal on the fourth day. At this time the patient was alert and the muscular pains and nuchal rigidity had dis-

appeared. He drank fluids readily. The rash faded gradually and on the sixth hospital day was petechial in nature, being most prominent on the soles of the feet. All signs and symptoms had disappeared by the eighth hospital day and the patient was discharged, apparently fully recovered on June 7, 1945, twelve days after admission.

Discussion

Dr. Hugh Davis. Rocky Mountain Spotted Fever, a rickettsial disease, was long recognized in the western United States but was not identified in the eastern section until 1930. One of the earliest cases studied in the Atlantic States was a patient admitted to Children's Hospital, Washington, D. C., in September 1930 and who subsequently died.

As in the case just presented, a history of exposure to ticks, with the latter often found attached to the skin, is of great assistance in arriving at a diagnosis. Ten of eighteen children in the Children's Hospital series reported by Dr. Harry A. Ong in 1940 (1) gave a history of exposure in tick infested areas. The vector of the disease in the eastern United States is the dog tick, *Dermacentor variabilis*. Twelve of the cases in Dr. Ong's series resided in suburban or rural Maryland, three were from nearby Virginia and three from the District of Columbia, the latter with history of exposure to ticks in Maryland. Fifteen of the eighteen were white children and the other three colored.

The outstanding characteristic of the disease is the rash which is usually maculopapular initially, and then later frequently becoming petechial or purpuric in character. Of great significance is the distribution. As a rule it begins on the hands and feet, often around the wrists and ankles, and is found on the soles and palms. It may later spread centripetally over the entire body. The rash makes its appearance early in the disease, usually on the second or third day.

Irritability, drowsiness, headache, vomiting, abdominal pain and tenderness and pain in the extremities are among the outstanding signs and symptoms. There is an attendant high sustained fever which generally remains above 103°; however, on occasion, the temperature may be of the remittent type.

The diagnosis of Rocky Mountain Spotted Fever is confirmed by agglutination of Proteus OX19 and complement fixation test.

Typhus fever must be differentiated. This is a disease of late summer and fall whereas Rocky Mountain Spotted Fever is more prevalent in spring and early summer. Cases of Typhus are usually urban residents with history of contact with rats; Rocky Mountain Spotted Fever cases are usually rural in tick infested areas. It is important to emphasize that a history of tick bite is frequently not elicited in Rocky Mountain Spotted

Fever. The incubation period of Typhus is longer and the rash is distributed over the chest and abdomen rather than on wrists and ankles and is seldom on the palms and soles and appears later than in Rocky Mountain Spotted Fever.

The treatment is largely supportive and symptomatic. The sulfonamides are ineffective and occasionally appear to produce untoward effects (2). Similarly penicillin does not appear to be particularly efficacious. There is some difference of opinion regarding the desirability of administering intravenous fluids. Topping (3) recommends that fluids be given by hypodermoclysis rather than by the intravenous route and similarly, Martin (2) concludes that blood transfusions probably are contraindicated because of the endarteritis which is one of the pathological features of the disease. However, Harrel et al. (4) believe that intravenous therapy, when properly chosen, is not harmful. These latter investigators state that because of the vascular lesions, the loss of circulating body fluids particularly protein, is analogous to that in burns, and peripheral circulatory collapse may develop if inadequate treatment is given. They recommend frequent plasma and blood transfusions together with glucose, saline and amino acids as indicated. In the case reported here, the patient received only one infusion of 300 cc. of 5% glucose in saline.

Immune serum should be given by intramuscular injection if the case is seen within the first five days of illness. Later in the disease, it is considered useless to administer the serum. Topping and Dyer state that no case which received the serum within five days of the onset of the disease has ended fatally. This patient, having been ill ten days when admitted, was not given serum. Most cases recover without much of any treatment, the disease usually running its course in about two weeks. It is not unlikely that there are some mild cases that go unrecognized or are called measles or one of the other exanthema. Oftentimes, however, even those who have the benefit of serum on the second or third day run a very severe and stormy course with continuous high fever, severe pain in the abdomen and extremities and extreme irritability. Mortality, however, is not as great as the prevailing impression would seem to indicate. In Dr. Ong's series of cases it was only 16%.

Prophylaxis is important in a tick infested area such as ours and the surrounding rural communities. The Cox vaccine grown on the yolk sac of the chick embryo is generally used. It is supplied by the United States Public Health Service through the local Health Department and is also obtainable from commercial drug firms. This year, unfortunately, the supply was exhausted before the demand for the vaccine was met. It should be administered early in April if protection is to be provided at the beginning of the season. Yearly vaccination is considered necessary

to keep up immunity. A word of warning should be noted as to the use of this vaccine in children with an allergy to eggs since it is grown in egg media. One fatality has been reported this year in such an allergic child. In cases where a history of egg allergy is elicited, vaccine prepared from macerated ticks may be employed.

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SPECIAL REPORT

INTUSSUSCEPTION

Howard S. Madigan, M.D.

Intussusception is an outstanding pediatric surgical emergency. Fortunately, it is not exceedingly common but, because of its severity and unfavorable prognosis if not recognized and treated as soon as possible, this condition merits prominent consideration in the discussion of acute abdominal conditions peculiar to children. The object of this paper is to review this clinical entity encountered at Children's Hospital between 1940 and 1944 and to elaborate on certain clinical features which deserve emphasis.

During the years 1940 and 1944 there were 31 cases of intussusception admitted to the hospital, an average of about six cases a year. In accord with reports in the literature, males were affected more frequently, a ratio of 2½ to 1 in the series (22 males, 9 females). Racial incidence shows a predominance among white children, 24 of the cases being in this group. The ratio of boys to girls in the white patients was 4 to 1, whereas in the colored group there were three males and four females. Observations of the seasonal distribution reveals that most of the cases occurred during the spring and summer months, twenty-one cases occurring between March and August.

Virtually all of the patients were well-nourished, healthy children who had been well prior to the onset of symptoms. The average age was 14 months although there were two cases in infants 3 and 4 months of age respectively. Eighteen patients were under one year of age, and fifteen of these were between 5 and 10 months old. There were six patients between the ages of 1 and 2 years, and the remaining seven patients were over two years old. The oldest patient was 3½ years and, interestingly enough, experienced a recurrence six months later. Such recurrences are quite rare, but in this case the findings at operation on both occasions substantiated the diagnosis.

The three cardinal manifestations of intussusception, namely, abdominal pain, vomiting, and the passage of blood-containing stools, occurred in the majority of cases. Vomiting occurred in the 31 cases and in many instances was the initial symptom. Abdominal pain was manifested in 21 cases and bloody stools were recorded in 23 cases. These three features were the outstanding ones in the histories obtained. Other manifestations included diarrhea, refusal of food, listlessness and moderate fever. One patient had recovered from pneumonia four weeks previously, while two others were recovering from episodes of diarrhea when the onset took place.

Despite the usual acute onset of this condition and the rapidity with which the symptoms and signs appear there is often considerable delay in making the diagnosis and hospitalizing these children. In the present series the average time from the onset of symptoms until admission to the hospital was 26 hours. Two cases went for as long as four days before admission; it is of interest to note that both were attended by a fatal outcome. It is cogent at this point to stress the urgency of hospitalizing these patients as soon as possible after the onset and establishment of the diagnosis.

At the time of admission, abdominal manifestations were prominent in most cases. Distention was moderate to marked and generalized tenderness noted in about one-half of the cases. In four cases the abdomen was soft and doughy without distention. Six of the patients were markedly toxic and dehydrated on admission. An abdominal mass was palpable in 16 of the cases, an incidence of 53.3%. In several instances, a rectal mass was palpable and blood was noted on the examining glove. No other remarkable physical findings were noted, although three of the patients presented evidence of mild upper respiratory infection.

Diagnosis was based almost wholly on the history and clinical manifestations. Flat plates of the abdomen were made, largely as a confirmatory measure, in nine instances. Eight of the films revealed evidence of intestinal obstruction and one film was essentially negative.

Following admission to the hospital, operation was performed in most cases with a minimum of delay. The average time from admission to operation was $5\frac{3}{4}$ hours. In general, either of two courses was followed, namely, immediate operation or institution of necessary supportive measures for a few hours prior to operation depending on the infant's general condition on admission. It should be noted that only cases in which an operation was performed are included in this series, inasmuch as this represents the only certain means of establishing the diagnosis of intusssusception.

In most cases the operation was limited to reduction of the intussusception. A Meckel's diverticulum was found and believed to be the inciting factor in two cases and was removed. Appendectomy was performed in thirteen cases after reduction of the intussusception. An enterostomy was necessary in one case. In another patient who had extensive gangrenous changes of the bowel a modified Mikulicz operation was done. Initially, the loop of bowel was exteriorized and the wound closed. At a subsequent date an anastomosis was successfully performed. The child, although only six and one-half months of age, recovered after a lengthy hospital course of 58 days. The average period of hospitalization in the series was 12 days, the case cited above being the maximum.

In the thirty-one cases there were four fatalities, a mortality rate of

12.9%. As previously mentioned, two of the patients had been ill for four days prior to admission, a factor which contributes immeasurably to a fatal outcome. These patients were both seven months of age. The other deaths were in infants of six months. Considering only infants, the mortality is 22.2%, while above the age of one year there was no mortality in this series. This is significant since 18 of the 31 cases were in the former group.

In the overwhelming majority of cases, the intussusception occurred at the ileo-cecal junction. There was one instance of an ileo-ileal type, and in one instance, the intussusception was confined to the colon.

Discussion

Intussusception, a condition in which a segment of intestine invaginates into an adjacent part, is one of the more common causes of intestinal obstruction in infants and young children. The prognosis is directly proportional to the duration of the condition, hence emphasis is placed on certain features of value in recognizing intussusception.

As revealed in the statistics of the present series, intussusception is most common in infants under one year of age, particularly during the latter half of the first year. Similarly, healthy white male children are most often affected. Only occasionally is there any history of illness immediately preceding the onset. Especially conspicuous is the absence of gastro-intestinal upsets, which might be supposed to be a likely preceding event.

The precise etiology of this condition is not known. In some cases the presence of tumors in the lumen of the bowel, such as plyps, have been indicated as the etiology. Less commonly, a Meckel's diverticulum is the inciting factor. In the great majority of cases, however, there is no demonstrable cause. It is possible that some transient disturbance of normal intestinal physiology occurs to incite the intussusception, which is then propagated by peristaltic activity.

Pathologically, the condition is a mechanical infolding of the bowel with resultant obstruction. The mesentery is carried along and circulatory disturbances ensue. The abnormal physiology which supervenes is similar to that occurring in intestinal obstruction from any cause. Two processes take place, namely, mechanical obstruction and interference with the blood supply of the involved portion of bowel. Edema and vascular changes occur with considerable rapidity and may, if not relieved, lead to gangrene and necrosis, followed by peritonitis and death.

There are four types of intussusception, based on the site of origin. By far the most common is the ileo-cecal variety, in which the ileo-cecal valve is the starting point of the intussusception, the cecum and appendix

being dragged in afterward. Next in frequency is the ileo-colic type, in which the process starts in the last few inches of ileum and continues into the colon. Decidedly less common are intussusceptions confined to the colon or to the small intestine. Rarely are compound or double intussusceptions encountered.

Mention has been made of the necessity of early recognition. Actually, any infant having bloody stools may be suspected of having an intussusception. Awareness of the frequent occurrence in healthy infants during the latter half of the first year of life is of value. The onset is usually abrupt. Severe, colicky abdominal pain is often the first manifestation. An apparently normal infant will suddenly scream or cry out with pain, become pale and thrash about in the crib. These episodes usually last but a few minutes, but recur with increasing frequency. In the interim the child is quiet and apathetic and becomes quite pale. Vomiting is usual and may be repeated and severe, contributing to the toxicity of the patient. Stools may be passed shortly after the onset and appear normal. Soon, however, the characteristic tenesmus and passage of blood-and-mucous stools occurs. The child becomes progressively toxic, vomiting increases, pallor is marked and exhaustion is evident. Fever is not prominent during the first 24 or 48 hours, but rises with the development of peritonitis.

Examination usually reveals a definitely toxic patient, temporarily quiet, pale and listless. Within the first 48 hours the abdomen may not show much distention and is often soft and doughy in consistency. A hard mass, characteristically described as 'sausage-shaped' may be palpable. Tenderness is usually not marked. Visible peristalsis may be incited by palpation, causing an episode of pain.

Rectal examination should never be omitted. Palpation of a mass per rectum is not consistently possible. However, on withdrawing the examining finger, a small amount of blood or blood and mucus, often having the typical "currant jelly" appearance, may be extruded or remain on the finger. This finding, in conjunction with the other clinical manifestations not infrequently renders the diagnosis of intussusception definite.

The use of a barium enema as a confirmatory diagnostic aid is not advised. It is rarely a necessity to establish the diagnosis, is not without danger, and introduces delay in relief of the intussusception. A flat plate of the abdomen will usually give the evidence of the existing intestinal obstruction.

The treatment of intussusception is surgical and should be undertaken directly after the diagnosis is established. Because of the toxic condition of most of these patients, a minimum of surgical procedure is indicated. In most cases opening of the peritoneal cavity and reduction of the intussusception is sufficient. This is accomplished by "milking out" the intus-

suscepted bowel. Difficulty may be encountered in reducing the last few inches, due to the edema, and gentle traction is required. The presence of any possible inciting factor, e.g., a polyp, Meckel's diverticulum or tumor, should be ascertained. The surgeon must judge the viability of the intussuscepted portion of the bowel. Occasionally it will be deemed necessary to resect a portion of the bowel because of gangrene and necrosis. Primary resection and anastomosis is attended by uniform failure. A two-stage procedure, a modification of the Mikulicz type of operation, is more successful. It was formerly taught that resection in infants was always fatal. However, one instance in the present series and a more recent case not included in this series in which the above mentioned two-stage procedure was successfully accomplished, lend encouragement to the prognosis in cases in which gangrenous bowel is encountered. Undoubtedly, a better understanding of intestinal physiology and the application of new methods of therapy, particularly in the realm of parenteral feeding, are responsible in a large measure for these successes. The routine removal of the appendix is not recommended.

The aim of treatment should be to correct the pathological changes and restore the infant's physiologic balance to normal as quickly as possible. Supportive care is of paramount importance. The administration of the electrolytes lost through vomiting, chiefly chlorides, can be accomplished by administration of physiological saline solution intravenously. A single blood transfusion post-operatively is of considerable value, even though no great amount of blood is lost. It is advisable to keep the intestinal tract empty for about 24 hours. When oral feeding is resumed, small quantities at frequent intervals should be give. The amount and interval should be increased until a normal diet is taken.

It is to be stressed that the mortality in these cases is, as a rule, not the result of surgical procedures, but stems from delay in instituting treatment and faulty post-operative management. Intussusception, an important pediatric emergency, may be successfully managed by prompt diagnosis, early surgical intervention and adequate post-operative care.

TRACHEO-BRONCHIAL CYST

Case Report No. 27

Dr. Frederic G. Burke W. W.—44-5192

W. W., age two weeks old, white male, was admitted to the hospital July 11, 1944 with the chief complaint of severe respiratory embarrassment and cyanosis.

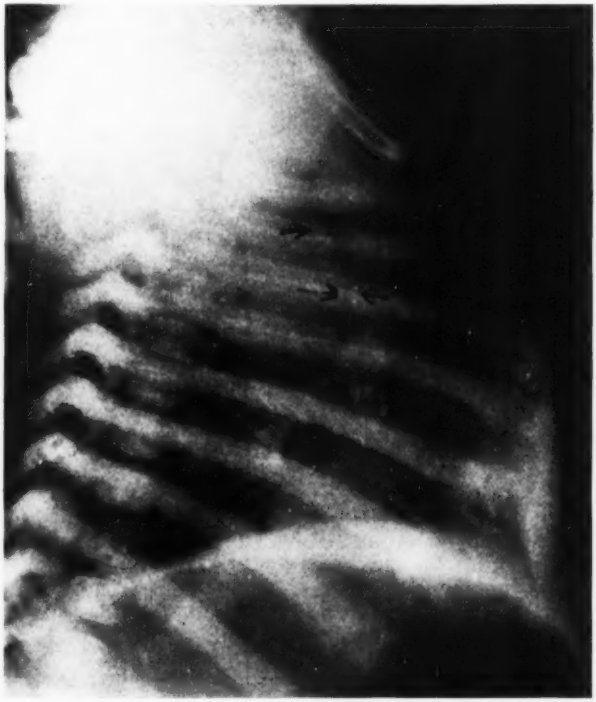
From birth, which had been normal, this infant had evidenced signs of atelectasis which lasted for three days. During this time he was placed in oxygen and received vigorous therapy calculated to stimulate respiration. A good response was noted at this time and he was sent home at the end of 10 days. The following day at home it was noted that respirations were of a diaphragmatic type and this persisted until the fourteenth day when respiration ceased entirely and cyanosis became quite marked. The infant was admitted in this condition, life having been supported by artificial respiration. Examination at this time revealed flatness over the entire right chest and hyper-resonance over the left. Breath sounds were diminished over the right. There was no lymphadenopathy and examination of the blood was normal. Respirations were re-established by means of stimulating drugs and oxygen carbon-monoxide mixture but was accompanied by marked extension of the head and retraction of the soft parts of the thorax. X-ray of the chest confirmed the impression of complete atelectasis of the right lung with compensatory emphysema of the left lung. The heart, mediastinum and trachea were shifted to the right. The infant seemed to make good progress after four days and was taken out of the oxygen tent and respirations appeared to be normal. A repeat x-ray examination of the chest on the second day after admission indicated some re-expansion of the collapsed lobe. The child was discharged on twenty-first of July, ten days after admission, vastly improved.

At home the infant again demonstrated respiratory difficulty with much wheezing and a slight cough. He occasionally exhibited periods of cyanosis and had to be revived by artificial respiration. After recovery, however, he seemed to be quite well and gained weight and was otherwise normal. This infant was re-x-rayed on August 4, following a severe episode of respiratory difficulty and a collapse of the left lung especially of the lower lobe with a marked shift of the heart and mediastinum was reported. A lateral view taken at this time and an examination of the esophagus, by means of barium, revealed the trachea and esophagus to be displaced anteriorly and somewhat to the right by a mass in the posterior mediastinum. The nature of this mass was not known, although the opin-

ion of a lympho-blastoma or congenital cyst was advanced, this being the cause of the paradoxical atelectasis.

During the next six weeks the infant was given a total x-ray irradiation dose of 750r without any apparent reduction in size of this mass.

He was again admitted to the hospital on September 4 with the same complaint, this time with a collapse of the left lung. Almost complete re-



TRACHEO-BRONCHIAL CYST

W. W.—Tracheo-bronchial cyst arising from the lower portion of the trachea and left bronchus. Note anterior displacement of these structures.

expansion of the affected lobe again took place, this time after about a week or ten days, and again respirations and general development appeared good. However, on the twenty-second of September the infant failed to survive a severe attack of respiratory collapse and cyanosis and succumbed.

Treatment during his stay was entirely supportive except for an attempted aspiration of the mass by Dr. Edgar Davis. This was done the

day before death in the hope that the mass was a cyst and could be collapsed by aspiration. The effort, however, was unsuccessful.

Necropsy Summary

The left lung was completely collapsed and the right lung was markedly emphysematous. The atelectatic left lung was apparently due to a cystic mass measuring 2 x 3 c.cm. which arose from the posterior wall of the carina and extended downwards along the left main stem bronchus. This mass contained 8 c.cm. of grayish thick mucous material which upon microscopic examination showed a few cholesterol crystals but no cells. The mass itself was grayish white in color and had a smooth lining. On section, the cyst was composed of crescents of fibrous tissue lined with well-differ-

Position of the Cyst
Arising from the trachea and left main bronchus

entiated bronchial epithelial cells, none of which were ciliated. The posterior wall of the left main bronchus was deficient of cartilage which resulted in obstruction of this bronchus by the mass when it pressed forward.

Discussion

Cystic tumors of the mediastinum are not uncommon, constituting by far the commonest group of tumors found in this region. Cysts arising from the tracheobronchial tree, however, are rare and comparatively few cases have been reported occurring in infancy.

Hare (1), in reviewing about 600 cases of mediastinal tumors that had been reported before 1899, found no record of this type of cyst. In 1937,

Alford (2) collected 7 cases only one of which had appeared in the American literature. Huer and Andrus (3) (1940) reviewed a total of 25 cases and reported one personal case. Robbins discussed the roentgenological aspects of the diagnosis of bronchogenic cysts in his review of the 15 cases he was able to collect from the files of the Massachusetts General Hospital during a ten year period, most of which were in adults. Marshall and Cookson (4) reported the case of such a cyst in a 7 months old infant almost identical to Alford's and to the case presented here. The majority of the cases reviewed occurred in adult patients and some were discovered only upon a routine examination, the cyst having caused no symptoms. Probably less than a half a dozen cases occurring in infants were of such a character as to result in death.

Tracheo-bronchial cysts probably originate from an embryonal plaque that is pinched off during the development of the bronchial tree. The clinical history and course of our patient would suggest that this cyst had been present from birth. Due to its position, the mass was able to alternately obstruct the right main bronchus as it did upon the first admission, resulting in collapse of that lung or obstruct the left bronchus as it did on subsequent occasions. Thus it acted in a pendulum-like fashion and accounted for the paradoxical atelectases. The entire anterior wall of the cyst formed the posterior wall of the lower portion of the carina, first portion of the right stem bronchus and for 1½ c.cm. of the left bronchus (see diagram). The absence of any supporting structures to resist the pressure of this mass permitted obstruction to occur and was incompatible with life.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by—Dr. E. Clarence Rice
Assisted by—Dr. John E. Cassidy

Held Every Tuesday Afternoon at 3:00 P.M.

HISTOPLASMOSIS

Case Report No. 28

Dr. John E. Cassidy F. C.—38-5549

F. C., a white girl aged 11 months, was admitted to Children's Hospital on July 22, 1938. The patient's illness dated from the early part of January 1938, when at the age of 6 months she had been weaned and given a formula containing cow's milk obtained from a cow owned by her parents. About three weeks later she began to have intermittent fever and projectile vomiting two or three times daily after feedings. One month prior to admission she exhibited marked drowsiness accompanied by periods of alternating diarrhea and constipation, with intermittent fever still persisting.

The past history was essentially negative. The patient was born prematurely at the age of 7 months, the birth weight being 3 pounds 14 ounces (1,780 gm). Labor was induced because of the mother's hypertension. The infant, apparently normal at birth, had developed satisfactorily until the onset of the last illness.

The family history was irrelevant. The parents were of English, Irish and German extraction and lived on a farm several miles from Paeonian Springs, Va. The mother's health had always been poor and she had suffered from "kidney trouble" since an attack of scarlet fever in late childhood. There were no siblings. Neither the parents, the patient nor the immediate associates had ever been out of the state of Virginia.

In summary, this infant was admitted with a history of intermittent fever and vomiting of six months' duration, drowsiness, and alternating diarrhea and constipation of one month's duration.

Physical examination on admission revealed a malnourished and slightly dehydrated child weighing $8\frac{4}{5}$ pounds (4 kg.). Temperature was 103.2°F. There was slight ptosis of the left eye and the teeth were absent. Bilateral cervical adenopathy was noted, as well as scaling of the skin of the hands and feet. Over the left lower costal area there was a slightly elevated soft white lesion measuring approximately 4 cm. in diameter. The heart rate was rapid, and a systolic murmur could be heard over the pulmonary areas. The spleen extended down to the iliac crest, and the liver was

palpable 6 cm. below the right costal margin in the midclavicular line. The remainder of the physical examination was essentially negative.

The urine was normal. Reactions to tuberculin (1:1,000), Schick, Wassermann and Kahn tests were all negative. Sternal puncture was attempted without success August 5, eight days before death. It was not repeated because of the critical condition of the patient.

The results of differential counts are shown in the accompanying table. No malarial parasites were seen on the blood smear. Marked anisocytosis and a few poikilocytes were evident. On the day before the infant died no thrombocytes were seen on smear. In view of the presence of hepatosplenomegaly and aberrant blood picture, a clinical diagnosis of aleukemic leukemia was entertained.

Hemograms

	JULY 22	JULY 27	AUG. 4	AUG. 9	AUG. 10	AUG. 12
Hemoglobin	5.0 gm. (30%)	10.5 gm.	9.5 gm.	9.5 gm.		
Red blood cells	2,140,000	3,240,000	3,810,000	2,900,000		
White blood cells	3,700	4,100	3,100	2,500		
Neutrophils	62%	67%	60%	64%	75%	75%
Segmented forms	57%	23%	44%	56%	36%	27%
Band forms	5%	29%	10%	6%	37%	38%
Metamyelocytes		15%	6%	2%	1%	10%
Lymphocytes	34%	31%	40%	32%	8%	
Monocytes	1%	2%		4%	5%	
Eosinophils	2%					
Plasma cells	1%					
Monocytic cells (possibly stem cells)					8%	
Unclassified cells					5%	

From the day of admission the patient's course was rapidly downward. Gavage feedings and nearly daily hypodermoclysis, intravenous infusions of dextrose and transfusions were required to maintain nutrition. For the first ten days following admission the temperature fluctuated between 98.6° and 103°F. From the tenth day on there was sustained pyrexia, the temperature ranging from 101° to 105°F. No increase in the size of the liver and spleen was noted during the hospital stay. Twelve days after admission, a decubitus ulcer 2 cm. in diameter appeared over the sacral area and gradually increased in size. Two days later a purpuric area measuring 4 cm. in diameter appeared on the left side of the abdomen and shortly thereafter a small gangrenous area the size of a pea was noted on the right ala nasi. These areas gradually became more extensive, and three days

later several small purpuric spots were seen around the umbilicus and in the left groin. The patient died on August 12, twenty-two days after admission and approximately seven months after the onset of illness.

Necropsy (Gross and Microscopic)

The body was 60 cm. long, which is normal for a baby of 4½ months. It weighted 3,580 gm. The skin contained areas of hemorrhage of varying size, the largest 2 cm. in diameter, with ulceration. Deep purple staining material was observed immediately below the epidermis and in the deeper portions. Parasitic bodies were present in these areas, being especially numerous at the points of ulceration. The skull was not opened. The cisternal fluid was clear and colorless.

The thymus and mediastinal and bronchial lymph nodes appeared normal on gross examination. The pleural cavities also appeared normal. The lungs showed congestion and atelectasis. The pericardial sac and heart were essentially normal as was the peritoneal cavity.

The liver, which weighed 237 gm. (normal, 175 gm.), was firmer than normal, with capillary hemorrhages and passive congestion. Microscopic examination revealed fibrosis about the trinities, with numerous and prominent cells of the reticuloendothelial system containing many parasitic bodies. There was a considerable deposition of brown pigment.

The spleen weighed 144 gm. (normal, 16 gm.) and was 11.9 cm. long. The surface was deep red and the cut surface firm and congested. There was extensive replacement of the lymph follicles by endothelial cells crowded by parasitic bodies and pigment. Although the reticulum was prominent, the trabeculae were not. The pancreas showed areas in which the acinar structures had undergone a fatty metamorphosis or replacement by foam-like cells which appeared to contain bodies suggestive of parasitic bodies.

In the intestine numerous petechiae were observed in the serosa, the vessels being injected. The mucosa was edematous, with hemorrhagic and ulcerated areas. Microscopic examination showed a dense infiltration of large cells containing parasitic bodies immediately beneath the ulcerated areas. The inflammatory reaction was mild. In the necrotic area was observed a mass of purple staining material similar to that noted in the skin and kidney.

The mesenteric lymph nodes were enlarged and matted together. Microscopic examination showed replacement of the original structure except the capsule and reticulum by very large foamlike cells containing parasitic bodies. Some cells were multinucleated and others showed no nuclei and were probably at the point of rupture.

The kidneys weighed 38.5 and 36 gm. (normal, 21 gm.), were congested and showed petechial hemorrhages. Small gray and white areas were

scattered throughout the cortex and medulla. Microscopic examination revealed collections of black or deep purple pigment in the vessels which showed intimal proliferation. The tubules showed degenerative changes, as evidenced by swelling and fatty infiltration of the lining cells, their lumens containing hyaline material and deep purple pigment.

In the adrenals, hemorrhagic and firm white areas were noted. The greater portion of the medulla and to a lesser extent the cortex were replaced by large clear pale staining cells with relatively small nuclei. These cells were largely filled with parasitic bodies rather than fat; however, many of the cortical cells showed evidence of fatty metamorphosis. Several areas of necrosis were found in the central portion of the gland.

In the bone marrow, endothelial cells containing parasitic bodies were frequently noted.

The parasitic bodies seen in sections of the skin, liver, spleen, pancreas, intestine, mesenteric lymph nodes, adrenals and bone marrow closely resembled the intracellular parasites described by Crumbine and Kessel. The organisms were found almost without exception in large endothelial cells. On examination with oil immersion, each body was found to consist of a central portion surrounded by a capsule or wall.

On first observation there appeared to be a rather marked similarity between the parasitic bodies and the Leishman-Donovan bodies of kala-azar. However, no distinct blephoroplast was observed, and the wall was thicker than the thin ectoplasmic membrane of parasitic bodies. The irregular arrangement of the chromatin material within the cytoplasm was more suggestive of a yeastlike body than of a protozoan cell.

Discussion

Dr. E. Clarence Rice. Our purpose in presenting this case of histoplasmosis is not to bring to your attention a rare disease, but rather to trace the evolution of a disease which prior to 1905 was unknown and possibly is quite common. Prior to and since 1905 it is probable that many patients were diagnosed as having kala-azar who actually had histoplasmosis. Darling (1) was able to demonstrate that an illness resembling kala-azar, characterized by splenomegaly, irregular pyrexia, leukopenia, anemia, emaciation and chronicity was due to a parasite which he designated as *Histoplasma Capsulatum*. Subsequent investigators have identified the parasite as a yeastlike organism by culture on Sabaraud's and other appropriate media.

The organism has a predilection for the cells of the reticulo-endothelial system and the various lesions found in patients are most often associated with the organs where such cells are most numerous, viz. spleen, lymph nodes, intestines and adrenals.

The case which has been reported was at first thought to be kala-azar and this diagnosis was concurred in by those familiar with tropical diseases. Fortunately DeCoursey at the Army Medical Museum and Lilly at the National Institute of Health had seen cases of histoplasmosis and were able to properly diagnose the lesions seen in the sections of the various organs. Shaffer, Shaul and Mitchell (2) subsequently reported this as the fourth case of histoplasmosis to be recorded in the United States.

Since then many cases have been reported in the literature and many more have been found throughout the world. Recently Dr. Virginia Cull, one of our former Residents in Pathology, stated that she had within a year examined biopsied material from the jaw and the epididymus and found evidence of histoplasmosis in two adults.

A recent article by Palmer (3) based on the examination of nurses showing calcification of the lungs by roentgen examination but demonstrated to have negative tuberculin tests is most interesting as suggesting that histoplasmosis may be much more common than we have believed it to be and may at times pursue a more benign course than we have formerly thought. This combined study made jointly by the National Tuberculosis Association and the United States Public Health Service included 3,105 nurses. These were tested with intradermal injections of histoplasmin, the latter a dilution of a filtrate of a broth culture of *Histoplasma Capsulatum*. Of this group 711 (22.9 per cent) showed a positive reaction to histoplasmin. The percentage of positive or doubtful reactors varied from 6.5 in Minneapolis and St. Paul to 65.8 in Kansas City, Mo.

The most interesting and important point brought out as a result of this investigation indicated a total of 294 individuals with pulmonary calcification. Of these, but 21.4 per cent had a positive tuberculin while of the remaining four-fifths (231) who had negative tuberculins, 206 or 78.5 per cent gave a positive or doubtful reaction to histoplasmin.

This data suggests that histoplasmosis may be much more prevalent than we have believed it to be and that the disease may not always terminate fatally. Certainly the use of histoplasmin as well as tuberculin would seem to be justified as a testing antigen in many cases as an aid to diagnosis of pulmonary and systemic disease.

The evolution of histoplasmosis from a rare and fatal disease to one which may follow a more variable course and may possibly be quite common is most intriguing.

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CLINICAL PROCEEDINGS OF THE CHILDREN'S HOSPITAL

Washington, D. C.

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Occasionally, the remarks and observations of guest speakers are included in this bulletin when thought to have particular interest. The proximity of the Children's Hospital to the Medical Centers of the Army, Navy and United States Public Health Service affords us the opportunity to invite many distinguished physicians to our conferences.

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BACKGROUND

THE use of cow's milk, water and carbohydrate mixtures represent one system of infant feeding that consistently, for over three dec has received universal pediatric recognition. No carbohydrate empl in this system of infant feeding enjoys so rich and enduring a backgr of authoritative clinical experience as Mead's Dextri-Maltose.